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10/586,072	07/14/2006	Douglas E. Brough	253625	7914

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EXAMINER	
SHEN, WU CHENG WINSTON	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/586,072	BROUGH, DOUGLAS E.	
	Examiner	Art Unit	
	Wu-Cheng Winston Shen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-34* is/are pending in the application.

4a) Of the above claim(s) *7 and 22-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6 and 8-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This application 10/586,072 is a 371 of PCT/US04/04891 filed on 02/19/2004, which is a Continuation-in-part of US application 10/373,249 filed on 02/24/2003, abandoned on 01/18/2007. Claims 1-35 are pending in the application.

Election/Restrictions

Applicant's election with traverse of Group II, claims 1-6 and 8-21, drawn to a method of changing the sensory perception of an animal, wherein the method comprises administering to the inner ear an expression vector comprising a nucleic acid sequence encoding an atonal-associated factor, wherein the nucleic acid sequence is expressed to produce the atonal-associated factor resulting in generation of sensory hair cells that allow perception of stimuli in the inner ear, wherein the expression vector is an *adenoviral vector*, in the reply filed on 5/31/07 is acknowledged. The traversal is on the ground(s) that sufficient similarity between the claims of Groups I-III to allow for the search and examination of the subject matter of all of the claims at the stone time without a "serious burden" being placed on the Examiner. Applicant asserts that there is no burden to search all the groups although the search may not be co-extensive. *This is not found persuasive* because the inventions are patentably distinct from each other for reasons set forth in the office action mailed on 05/01/2007. Inventions I-III are directed to related methods. The related inventions are distinct if the (1) the inventions as claimed are either not capable of use together or can have a materially different design, mode of operation, function, or effect; (2) the inventions do not overlap in scope, i.e., are mutually exclusive; and (3) the inventions as claimed are not obvious variants. See MPEP § 806.05(j). In the instant case, the

inventions as claimed have different starting materials, different method steps, and/or different goals. Furthermore, the inventions as claimed do not encompass overlapping subject matter and there is nothing of record to show them to be obvious variants. Thus, a search of all the groups in a single application is burdensome.

In response to the election of species requirement, Applicants elect, with traverse, the species nerve growth factor. However, upon further consideration, the requirement of election of species between brain-derived neurotrophic factor (BDNF) and nerve growth factor recited in claim 15 is withdrawn because BDNF is a member of nerve growth factor family of neurotrophic factors.

The requirement is still deemed proper and is therefore made FINAL.

Accordingly, claims 7 and 22-34 are withdrawn from consideration for being directed to non-elected subject matter.

Status of claims: Claims 1-6 and 8-21 are currently under examination.

Specification

The specification filed on 07/14/2006 stated CROSS-REFERENCE TO RELATED APPLICATIONS as follows: This patent application claims the benefit of International Patent Application No. PCT/US2004/004891, filed February 19, 2004, which claims the benefit of pending U.S. Patent Application No. 10/373,249 filed February 24, 2003. However, this statement appears to be incorrect and contradicts to the Application Data sheet (ADS) filed on 07/14/2006. Based on the ADS, this application 10/586,072 is a 371 of PCT/US04/04891 filed on 02/19/2004, which is a CIP of the US application number 10/373,249, filed on 02/24/2003.

To claim the benefit of U.S. Patent Application No. 10/373,249 filed on 02/24/2003, which is abandoned on 01/18/2007, appropriate correction is required, See 37 CFR 1.9.

Claim Rejections - 35 USC § 102/103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1. Claims 1, 3, 4, 16-20 are rejected under 35 U.S.C. 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Zheng et al (Zheng et al., Overexpression of Math1 induces robust production of extra hair cells in postnatal rat inner ears. *Nat Neurosci.* 3(6): 580-6, 2000; listed as reference FF on the IDS filed by Applicant on 11/16/2006).

With regard to claims 1, 3, 4, 19 and 20 of instant application, Zheng et al. reported that overexpression of Math1, a mouse homolog of the *Drosophila* gene atonal, from a plasmid,

which is an expression vector, in postnatal rat cochlear explant tissues resulted in extra hair cells. Zheng et al. found that the source of the ectopic hair cells was columnar epithelial cells located outside the sensory epithelium in the greater epithelial ridge, which normally give rise to inner sulcus cells. Moreover, Math1 expression also facilitated conversion of postnatal utricular supporting cells into hair cells. Examination of the whole mount and cross sections of the cultures one to two days after transfection revealed transfection of the columnar epithelial cells in the GER (See Fig. 2a and 2b, pages 581-582, Zheng et al., 2000), indicating ectopic hair cells are derived from greater epithelial ridge (GER) cells. Zheng et al. also taught the therapeutic application by administering a vector expressing Math1 in mammalian cochleae (i.e. a hollow tube in the inner ear of higher vertebrates that is usually coiled like a snail shell and contains the sensory organ of hearing) for treating hearing and balance disorder *in vivo* (See third paragraph, left column, page 585, Zheng et al., 2000). Zheng et al. concluded that Math1 was sufficient for the production of hair cells in the ear, and immature postnatal mammalian inner ears retained the competence to generate new hair cells (See abstract, Zheng et al., 2000).

With regard to therapeutic effect by expressing Math1 in treating hearing loss and balance disorder (claims 16-18 of instant application), Zheng et al. disclosed that hair cell loss due to noise and ototoxic damage is one of the major causes of *hearing and balance impairments* and the findings that overexpression of *Math1* can lead to robust production of extra hair cells in postnatal rat cochleae (i.e. inner ear) have therapeutic significance (See third paragraph, left column, page 585, Zheng et al., 2000).

While Zheng et al. did not explicitly teach, with provision of a working example, the therapeutic application by administering a vector expressing Math1 in mammalian cochleae (i.e.

in the inner ear) for treating hearing and balance disorder *in vivo,* it is noted that the teachings presented by Zheng et al. in explant tissues *in vitro* and the discussions on the therapeutic application *in vivo* render the claimed invention *prima facie* obvious.

Thus, Zheng et al. either anticipate claims 1, 3, 4, 16-20 under 35 U.S.C. 102(b) or, in the alternative, render claims 1, 3, 4, 16-20 of instant invention *prima facie* obvious under 35 U.S.C. 103(a).

2. Claims 1-6 8-10 and 16-21 are rejected under 35 U.S.C. 102(e) as being anticipated by Zoghbi et al. (US patent 6,838,444, issued Jan. 4, 2005).

The claims are drawn to a method of changing the sensory perception of an animal by administering to the inner ear an expression vector comprising a nucleic acid sequence encoding an atonal associated factor, wherein the expression of said factor results in generation of sensory hair cells that allow perception of stimuli in the inner ear. The claims are further drawn to said method wherein the animal is a human, the atonal associated factor is MATH1, HATH1, the vector is a viral vector, an adenoviral vector, an adeno-associated viral vector, replication deficient (E1) adenoviral vector, and the hearing cells are generated from adult differentiated cells such as scarred epithelia of inner ear. Claim 21 is further drawn to such a method wherein the viral vector comprises a moiety that binds to epithelia cell receptor and facilitates the transduction of said vector.

Zoghbi et al. disclose a method of generating hair cells for an animal comprising delivering directly to an inner ear of said animal an atonal associated nucleic acid encoding a

polypeptide having at least about 80% identity to MATH1 (SEQ ID NO: 58) (see lines 15-22, col. 1 and col. 139, claims 1-8). Zoghbi et al. also disclose such a method wherein the animal is a human, the atonal associated factor is MATH1, HATH1, the vector is a viral vector, an adenoviral vector, an adeno-associated viral vector, replication deficient (E1) adenoviral vector, and the hair cells are generated from adult differentiated cells of inner ear (see col.139, claims 1-8, and col. 47, lines 37-56, col. 48, example 16). Zoghbi et al. further disclose that different methods of delivery can be utilized to administer a vector into a cell. Examples include: (1) methods utilizing physical means, such as electroporation (electricity), a gene gun (physical force) or applying large volumes of a liquid (pressure); and (2) methods wherein said vector is complexed to another entity, such as a liposome, viral vector or transporter molecule (which binds to cell surface receptor, see col. 27, 2nd paragraph) (reading on claim 21 of instant application).

With regard to therapeutic effect by expressing Math1 in treating hearing loss and balance disorder (claims 16-18 of instant application), Zoghbi et al. teach methods of treating an animal, including a human, for cerebellar granule neuron deficiencies, for generating hair cells, for treating hearing impairment or an imbalance disorder by administration of a vector expressing the atonal associated factor (MATH1 or HATH1) (See for instance, second paragraph, col. 5).

With regard to sensory hair cells generated from adult differentiated cells of inner ear, from epithelia of inner ear (claims 19 and 20 of instant application), Zoghbi et al. teach, for instance, light micrographs of semi-thin transverse sections of inner ear sensory epithelia in

wild-type mice (See Figures. 3A, 3C, and 3E) and Math1$^{\beta\text{-Gal}/\beta\text{-Gal}}$ (See Figures. 3B, 3D, and 3F) mouse.

Thus, Zoghbi et al. clearly anticipate claims 1-6, 8-10 and 16-21 of instant application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 1, 6, 8-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zoghbi et al. (US patent 6,838,444, issued Jan. 4, 2005), taken with Kovesdi et al (US patent 6,821,775, issue date, Nov. 23, 2004).

The claims are drawn to a method of changing the sensory perception of an animal by administering to the inner ear an expression vector comprising a nucleic acid sequence encoding an atonal associated factor, wherein the expression of said factor results in generation of sensory hair cells that allow perception of stimuli in the inner ear, wherein the adenoviral vector used to deliver the nucleic acid is deficient in at least E4, E1 and E4, or E1 and E4 and further comprise a spacer in the E4 region.

The teachings of Zoghbi et al are set forth in the rejection under 35 U.S.C. 102(e) as being anticipated by Zoghbi et al. (US patent 6,838,444, issued Jan. 4, 2005).

However, Zoghbi et al. do not teach such a method wherein an adenoviral vector deficient in both E1 and E4 and further comprising a spacer in E4 region.

Kovesdi et al. teach a replication deficient adenoviral vector with deletion of E1 and E4 and further comprise a pGUS spacer in the E4 region (see second paragraph, col. 7 and claim 1). Kovesdi et al. further disclose that said vector is used to deliver therapeutic effective amount of PEDF to eyes of mice to promoter neovascularization.

It would have been obvious to one of ordinary skill in the art to use the adenoviral vector taught by Kovesdi et al. in the method of generating hair cells to deliver atonal associated nucleic acid to inner ear of a subject taught by Zoghbi et al. since the vector taught by Kovesdi et al. successfully delivers the PEDF *in vivo,* as such, the ordinary artisan would have been motivated to use this vector to deliver atonal associated nucleic acid *in vivo* because its effectiveness in expressing the gene of interest *in vivo*. The level of skill in art of molecular cloning is high. Absent evidence from the contrary, one of ordinary skill in the art would have reasonable expectation of success to replace the PEDF with an atonal associated nucleic acid sequence such as Math1, and deliver it to inner ear to generate sensory hair cells. Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

4. Claims 1, 13-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zoghbi et al. (US patent 6,838,444, issued Jan. 4, 2005), taken with Staecker et al. (Staecker et al., Brain-derived neurotrophic factor gene therapy prevents spiral ganglion degeneration after hair cell

loss. *Otolaryngol Head Neck Surg.* 119(1): 7-13, 1998; listed as reference EU on the IDS filed by Applicant on 11/16/2006).

The claims are drawn to a method of changing the sensory perception of an animal by administering to the inner ear an expression vector comprising a nucleic acid sequence encoding an atonal associated factor, wherein the expression of said factor results in generation of sensory hair cells that allow perception of stimuli in the inner ear, wherein said method further comprise administering to the inner ear a viral vector comprising a nucleic acid sequence encoding a neurotrophic agent such as brain-derived neurotrophic factor or nerve growth factor.

The teachings of Zoghbi et al are set forth in the rejection under 35 U.S.C. 102(e) as being anticipated by Zoghbi et al. (US patent 6,838,444, issued Jan. 4, 2005).

However, Zoghbi et al. do not teach such a method wherein a viral vector comprising a nucleic acid sequence encoding a neurotrophic agent such as brain-derived neurotrophic factor or nerve growth factor is also administered with the atonal associated factor.

Staecker et al. teach brain-derived neurotrophic factor (BDNF) gene therapy prevents spiral ganglion degeneration after hair cell loss by supporting the survival of auditory neurons (see abstract, bridging paragraph between left and right columns, page 10, and Figure 5).

It would have been obvious to one of ordinary skill in the art to co-administer neurotrophic agent such as BDNF with atonal associated factor in the method of changing sensory perception based on the combined teaching of Zoghbi et al. and Staecker et al. One of ordinary skill in the art would have been motivated to include BDNF in the claimed method because it has been shown by Staecker et al. to support the survival of auditory neurons. If the ordinary artisan intends to generate hair cells and improve hearing after hearing loss, the

ordinary artisan would be motivated to preserve the auditory neurons which is vital for hearing. The level of skill in the art is high. Absent evidence from the contrary, one of ordinary skill in the art would have reasonable expectation of success to co-administer the BDNF with atonal associated factor using separate or same vector in the method taught by Zoghbi et al. Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

5. No claim is allowed.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the Supervisory Patent Examiner, Peter Paras, can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications

may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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